CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS:

In the 10/24/02 submission, you provided datasets in

- Combo-PPK1
- Combo-PPK2
- Combo-PPD-1
- Combo-PPD-2
- JMCH-ComboPK
- jmch-ComboPPK

and in the 3/24/03 submission they included the datasets for

- JMAW-a-I

Currently, the PK data (and the PD data) are provided as one large file (in each of the cases listed above). We would appreciate it if you submit the specific PK datasets (and PD, as applicable) used for the modeling, along with their corresponding control streams and output files.

Please note that the datafiles should be submitted as SAS transport files (.XPT) and the control streams and output files should be submitted as ascii text files (.txt)

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/s/

Patricia Garvey
8/22/03 04:52:13 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	2	**Date:**	August 14, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please provide the following request from the medical officer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL

1. Please provide the CT scan report at baseline and visit #4 for patient #403-4047. Please provide translations as indicated.

2. For the following case, although the response evaluation by the independent readers may have been scored as PR for best overall response, the independent reader or readers' numbers/calculations do not indicate confirmed PR: #851-8518. Please clarify.

3. There were 118 patients, who were consented and entered but were not enrolled and randomized on JMCH. Please provide the specific reasons for not enrolling and randomizing these patients as indicated on The ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT form (p. 1179-1181).

APPEARS THIS WAY
ON ORIGINAL

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Patricia Garvey
8/14/03 05:33:30 PM
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Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	July 31, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please refer to NDA 21-462. The following is a request from the medical officer.

Please clarify the following queries in the JMCH dataset:

1. In EPISODE.XPT, there is a discrepancy between the codes for SEVRITYC given in the CRF, where the code 4 refers to grade 4 toxicity and SEVRITYZ, where code 4 is death. Please clarify.
2. In the Cycle delay, Hospital and Patient summaries tables, there does not seem to be any explanation of the various codes used under EPICODE. Please give the medical condition for each epicode.
3. In the HOSPITAL.XPT file the ADMFLG codes do not correlate with the codes in the CRF (codes 1 or 2). Please explain.
4. Please submit an explanation of the codes under EVCDE in TRANSFUS.XPT.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
8/1/03 09:14:08 AM
CSO
Facsimile sent to sponsor on July 31, 2003

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	2	**Date:**	July 28, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please provide the following request from the medical officer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL

1. For patients: #101-1017, #140-1451, #215-2151, and #302-3022, please provide the CT scan reports for baseline. Also, for patient #804-8055, please provide the CT scan reports for baseline, and visits #2 and #3. Please provide translations as indicated.

2. Please provide the missing images for visit 105 for patient #107-1071 are not in the imaging package provided to Dr. Mills (CBER).

3. For the following cases, although the response evaluation by the independent readers may have been scored as PR for best overall response, the independent reader or readers' numbers/calculations of the numbers do not indicate PR: #107-1072, #111-1344, #136-1631, #301-3170, #306-3103, #308-3178, #402-4029, #407-4125; #410-4182; #501-5061, #505-5041; and #852-8532. Please clarify.

4. Please provide a list of patients that were fully supplemented, partially supplemented, and never supplemented. A table, as shown below, may provide the requested information. Alternatively, please indicate the location of a table in the NDA with this information for individual patients.

SITE#-PATIENT#	SUPPLEMENTATION STATUS

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/s/

Patricia Garvey
7/28/03 01:38:28 PM
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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	2	**Date:**	July 3, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please provide the following request from the medical officer for NDA 21-462 Alimta.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL: INFORMATION REQUESTS

1. For patient: #850-8503, please provide the CT scan reports for baseline and first follow-up evaluation. Please provide translations as indicated.

2. Please provide the missing images for patients: #804-8040 and #804-8044. These were not in the imaging package provided to Dr. Mills (CBER).

3. The following cases were scored as SD for best overall response by the independent readers but are listed as responders:# 130-1191, #131-1272, #409-4170 #509-5133, #510-5147, #511-5151, #512-5112, #554-5516, #721-7225, #722-7251, #805-8070, and #851-8517. Please clarify.

4. For the following cases, although the response evaluation by the independent readers may have been scored as PR for best overall response, the independent reader or readers' numbers or evaluations do not indicate PR: #510-5103 and #510-5141. Please clarify.

5. The following case was scored as UK (unknown) for best overall response by the independent readers but is listed as a responder: #510-5143. Please clarify.

6. The following case was scored as PD for best overall response by the independent readers but is listed as a responder: #804-8055. Please clarify.

7. What was in the information packet (i.e., information about the patient, treatment arm, response @ the site) that the independent readers received prior to reviewing the CT scans? What was in the information packet (i.e., information about the patient, treatment arm, response@ the site, other readers' evaluations) that the adjudicator received prior to reviewing the CT scans?

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/s/

Patricia Garvey
7/3/03 02:29:22 PM
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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	June 30, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please provide the following request from the medical officer.

1. For patients: #302-3025, #512-5113, #554-5517, and #601-6012, please provide the CT scan reports for baseline and first follow-up evaluation. Please provide translations as indicated.

2. Please provide the missing images for the following patients: #114-1402, #124-1201, #136-1634, #142-1472, #201-2187 (in error, previously requested #201-2188), #201-2191, #301-3159, #301-3161, #510-5109, #510-5144, #513-5121, #552-5508, #558-5537, #558-5538, #558-5541, #601-6005, #601-6007, #601-6008, #601-6010, #601-6011, and #601-6014.

3. The following case was scored as SD for best overall response by the independent readers but is listed as a responder: #505-5042 (calculates as PD). Please clarify.

4. The following cases did not have review by the independent readers: #502-5052, # 601-6007, and #851-8512. Please clarify.

5. Please identify (i.e., patient #) the patient and/or patients whose scans were presented at the 2002 ASCO plenary session (Abstract #5).

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
7/1/03 03:32:34 PM
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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: John Worzalla - Eli Lilly and Company	**From:** Patty Garvey, R.Ph.
Fax: 317-276-1652	**Fax:** (301) 594-0498
Phone: 317-276-5052	**Phone:** (301) 594-5766
Pages (including cover): 1	**Date:** June 23, 2003
Re: NDA 21-462 Alimta	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please provide the following request from the medical officer.

1. For patients: #104-1045, #501-5061 and #720-7205, please provide the CT scan reports for baseline and first follow-up evaluation. Please provide translations as indicated.

2. Please provide the missing images for the following patients: #101-1017, #104-1043, #107-1074, #109-1092, #111-1342, #111-1354, #111-1357, #112-1290, #453-4519, #501-5007, #501-5062, #502-5017 and #502-5054. These were imaging package were not provided to Dr. Mills (CBER).

3. The following cases were scored as SD for best overall response by the independent readers but are listed as responders: #3-3001, #107-1073, #125-1217, #141-1461, #501-5006, and #503-5022. Please clarify.

4. The following case was scored as PD for best overall response by the independent readers but is listed as a responder: #401-4011. Please clarify.

Also, in the JMCH dataset, which Table and Columns should we use to replicate Table 6 (Selected Adverse Events) in the package insert.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
6/23/03 03:36:54 PM
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Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	June 19, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please provide the following request from the medical officer.

1. For patients: #131-1286, #410-4182, #451-4507, and #403-4048, please provide the CT scan reports for baseline and first follow-up evaluation. Please provide translations as indicated.

2. Please provide the following missing patients' images, which were not provided to Dr. Mills (CBER).

   #213-2133, #214-2148, #214-2401, #402-4025, #402-4036, #409-4333, #413-4241, #413-4243, and #413-4244 are not in the imaging package provided to Dr. Mills (CBER).

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
6/19/03 04:33:07 PM
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Fax

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Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	June 10, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

- **Comments:**

John,

Please provide the following request from the medical officer.

For patients : #102-1024, #130-1192, #130-1270, #306-3103, #308-3180, and #407-4125, please provide the CT scan reports for baseline and first follow-up evaluation. Please provide translations as indicated.

The images for patients #102-1022, #118-1133, #126-1222, #141-1463, #150-1580, #150-1582, #201-2188, #201-2200, #409-4164, and #502-5017 are not in the imaging package provided to Dr. Mills (CBER). Please provide these missing images.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
6/11/03 10:03:25 AM
CSO
Facsimile faxed to sponsor on June 10, 2003

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Jeffrey R. Ferguson – Eli Lilly & Co.	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1887	**Fax:**	(301) 594-0498
Phone:	317-433-5615	**Phone:**	(301) 594-5766
Pages (including cover):	2	**Date:**	May 30, 2003
Re:	NDA 21-462 Alimta® facsimile submission dated 5/29/03		

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jeff,

Please refer to your facsimile submission dated May 29, 2003 regarding chemistry issues.

Dr. Lostritto has completed the review of your submission and has the following responses to your questions.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

FDA RESPONSES TO CHEMISTRY QUESTIONS:

1. Will the lack of a DMF reference or a current inspection of the — site delay approval of Alimta?

   FDA: In general, the lack of a DMF reference will not result in a delay if complete and adequate information for the referenced item or process is otherwise provided in your NDA application at the time of submission. (In this usage, submission refers to when an NDA is filed as a single entity, or when the CMC sections are submitted as part of a rolling submission.) In the specific case of your to-be-marketed , — processes, we recommend that complete validated information, adequate to support a review on your behalf, be provided in your application if it is not accurately, completely and adequately described in a referenced DMF. If this information is not available in some appropriate manner, it is likely to have a negative impact on your review. Furthermore, at the time of NDA submission, all sites should be ready for inspection for all current to-be-marketed activities. Lack of inspection readiness at the time of NDA submission will almost certainly have a negative impact on the progress of your review.

2. Does FDA find the proposed submission strategy acceptable for the approval of Alimta?

   FDA: It is premature to comment in full regarding your planned post-approval activities for Alimta. Although your approach appears reasonable at this time, the acceptability and approval of your plan are review issues that we will manage when and if a supplement is submitted.

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/s/

Patricia Garvey
5/30/03 04:54:03 PM
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DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	April 30, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please provide the following missing images for patients #502-5052 and #851-8512. They are not in the imaging package provided to Dr. Mills (CBER).

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
4/30/03 04:51:17 PM
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Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	January 31, 2003
Re:	NDA 21-462 Alimta – Email dated 1/28/03		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

John,

Please refer to NDA 21-462 Alimta email dated January 28, 2003 requesting clarification to our facsimile dated January 24, 2003 regarding request for additional pathology reports. The following are responses from the clinical reviewer to your email.

For clarification of "confirmation documentation" and the FDA's request for this information, Lilly should refer to their letter to the FDA dated 1/10/2003 and their comment:

> "One of the entry requirements for study JMCH was to have local pathologic confirmation of malignant pleural mesothelioma. This requirement was validated by independent (independent from the site) monitors who were fluent in the local language."

Also, Lilly has not addressed the other component of the FDA's request for pathology reports:

> "The original and translations of the pathology reports for JMCH and JMDR from the other countries should follow as soon as possible. "

Please contact me if you have any questions.

Sincerely,

Patty Garvey, Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
2/6/03 10:33:10 AM
CSO
Fax sent to sponsor January 31, 2003

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	2	**Date:**	January 24, 2003
Re:	NDA 21-462 Alimta – Submission dated 1/10/03		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please refer to NDA 21-462 Alimta submission dated January 10, 2003 regarding your response to our facsimile dated December 19, 2002 requesting pathology reports from studies JMCH and JMDR.

The medical officer has completed the review of your submission and have requested the additional information.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

Does DODP agree with the sponsor's alternative proposal to provide the US pathology reports only (since the majority of the foreign pathology reports are in a language other than English)?

FDA: No. Please provide:

- **the pathology reports for JMCH from the U.S., United Kingdom, Australia, and Canada (in Canada, at least the English-speaking site[s]) sites.**
- **the pathology reports for JMDR from the U.S. and United Kingdom.**
- **the pathological confirmation documentation for all the patients entered on JMCH .**
- **for JMDR, the independent centralized pathology reviews for all the patients.**

The original and translations of the pathology reports for JMCH and JMDR from the other countries should follow as soon as possible.

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/s/

Patricia Garvey
1/24/03 03:56:26 PM
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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla – Eli Lilly & Co.	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	2	**Date:**	January 23, 2003
Re:	NDA 21-462 Alimta® submission dated 1-21-03		

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- **Comments:**

John,

Please find attached the meeting specifics for our upcoming Alimta meeting with Dr. George Mills.

Dr. Mills has requested that the meeting be scheduled for the whole day. The morning session will be for the imaging reading and afternoon session for follow-up discussion.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

MEETING SPECIFICS

The meeting to discuss Alimta® (LY231514 or pemetrexed) with Dr. George Mills as detailed in your January 21, 2003 submission is scheduled as follows:

Date	Day	Time	Location
February 4, 2003	Tuesday	9:00 am – 4:00 pm	Woodmont Office Complex 1 (WOC1) 1401 Rockville Pike, Rockville,MD

ATTENDEES

The anticipated attendees are:

George Mills, M.D., CBER – Clinical Reviewer

Additionally, the following person has been invited to attend the meeting:

John Johnson, M.D., Clinical Team Leader
Robert White, M.D., Clinical Reviewer

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/s/

Patricia Garvey
1/29/03 03:44:49 PM
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Fax sent to sponsor January 23, 2003

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DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla – Eli Lilly & Co.	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	2	**Date:**	January 23, 2003
Re:	NDA 21-462 Alimta® submission dated 1-21-03		

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please find attached the meeting specifics for our upcoming Alimta teleconference with the statistical team.

The telephone number where you can be contacted for the teleconference should be provided to me prior to February 5, 2003.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

MEETING SPECIFICS

The teleconference to discuss Alimta® (LY231514 or pemetrexed) with the statistical team as detailed in your January 21, 2003 submission is scheduled as follows:

Date	Day	Time
February 5, 2003	Wednesday	11:00 am – 12:00 pm

ATTENDEES

The anticipated attendees are:

Gang Chen, Ph.D., Statistical Team Leader
Yong-Cheng Wang, Ph.D., Statistical Reviewer
Patty Garvey, R.Ph., Project Manager

Additionally, the following person has been invited to attend the meeting:

John Johnson, M.D., Clinical Team Leader
Robert White, M.D., Clinical Reviewer

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/s/

Patricia Garvey
1/29/03 03:34:36 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Debasish Roychowdhury, M.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-433-2255	**Fax:**	(301) 594-0498
Phone:	317-433-6604	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	December 19, 2002
Re:	NDA 21-462 Alimta – Submission dated 10/25/02		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dr. Roychowdhury,

The following is a request from the clinical reviewer:

> Please provide the pathology reports from studies JMCH and JMDR from which the initial pathological diagnosis was made.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
12/19/02 04:17:18 PM
CSO

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DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Debasish Roychowdhury, M.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-433-2255	**Fax:**	(301) 594-0498
Phone:	317-433-6604	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	November 29, 2002
Re:	NDA 21-462 Alimta – Submission dated 10/25/02		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dr. Roychowdhury,

Please refer to your rolling NDA 21-462 Alimta submission dated October 25, 2002. Please provide the following requests to assist our statistician in the review of your application.

1. SAS programs for Table JMCH.11.3 to Table JMCH.11.81. in JMCH study.

2. Analysis SAS data sets to run the SAS programs of item 1.

3. SAS format program for all data sets of JMCH study.

The requests should be submitted by email to me and in CD disk to EDR. Please let me know if you have any question.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
11/29/02 12:18:15 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Debasish Roychowdhury, M.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-433-2255	**Fax:**	(301) 594-0498
Phone:	317-433-6604	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	November 19, 2002
Re:	NDA 21-462 Alimta – Submission dated 10/25/02		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dr. Roychowdhury,

Please refer to your rolling NDA 21-462 Alimta submission dated October 25, 2002. Please clarify the following comments from the clinical reviewer.

> Neither the Protocol nor the Study Report makes clear how the unidimensional pleural rind measurements are used in the calculation of objective tumor response. Is each pleural rind unidimensional measurement considered a separate lesion? Are all of the unidimensional pleural rind measurements added together to make one unidimensional lesion? Are the all of the pleural rind measurements added together with other unidimensional lesion measurements? If so, it would seem that tumor response is dominated by the multiple pleural rind measurements to the exclusion of non pleural rind tumors. A couple of illustrative examples would be helpful.

I am also the new project manager assigned to this NDA, therefore please contact for any issues regarding this NDA.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
11/19/02 01:48:27 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	John Worzalla – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-5052	**Phone:**	(301) 594-5766
Pages (including cover):	3	**Date:**	November 17, 2003
Re:	NDA 21-462 Alimta		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

John,

Please refer to your NDA 21-462 Alimta. Please address the following request from the clinical reviewer:

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL

1. Both independent reviewers did not evaluate any measurable disease in the images for the patients listed in the table below. Please clarify.

PATIENT #
119-1141
130-1266
131-1286
140-1450
302-3023
409-4332
453-4512
453-4513
453-4514
453-4515
453-4516
502-5055
503-5024
510-5110
512-5111
720-7203
804-8055
851-8519
852-8521
852-8523

2. One of the independent reviewers did not evaluate any measurable disease in the images for the patients listed in the table below. In nine of the cases, two out of three independent reviewers did not evaluate any measurable disease. Please clarify.

PATIENT #
103-1031
113-1301
114-1403
119-1144
119-1147
125-1216
141-1461
142-1475
301-3155
301-3162

302-3022
302-3024
302-3025
308-3180
401-4004
401-4014
402-4301
451-4509
452-4502
501-5008
501-5061
502-5014
502-5020
505-5046
510-5143
510-5147
512-5116
557-5531
601-6009
601-6013
720-7200
720-7206
720-7212
721-7225
804-8047
850-8503
851-8511

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/s/

Patricia Garvey
11/17/03 04:14:56 PM
CSO

TELECONFERENCE MINUTES

MEETING DATE: July 9, 2003 **TIME:** 11:25 am **LOCATION:** WOC2/rm 2064

NDA: 21-462

DRUG: Alimta® (pemetrexed, LY231514)

SPONSOR/APPLICANT: Eli Lilly & Company

TYPE of MEETING:

1. Guidance

2. **Proposed Indications:** Mesothelioma

FDA PARTICIPANTS:

Richard Pazdur, M.D.	--	Director, Division of Oncology Drug Product (DODP)
Grant Williams, M.D.	--	Deputy Director, DODP
John Johnson, M.D.	--	Medical Team Leader
Robert White, Jr., M.D.	--	Medical Reviewer
Maitreye Hazarika, M.D.	--	Medical Reviewer
Patty Garvey, R.Ph.	--	Project Manager

INDUSTRY PARTICIPANTS:

Binh Nguyen, M.D., Ph.D.	--	Alimta Medical Director
Paolo Paoletti, M.D.	--	Vice President, Oncology Platform Team
Brian Stuglik	--	Dir. of Project Mgmt, Oncology Platform Team
Sheila Swain	--	Clinical Development Associate, Alimta Team
David Rauh	--	Clinical Diagnostic Services Associate
Debasish Roychowdhury, M.D.	--	Director US Regulatory Affairs Director
John Worzalla	--	Alimta Regulatory Scientist

BACKGROUND:

The Division is currently reviewing a rolling NDA 21-462 Alimta for mesothelioma. The first piece of the rolling submission was submitted on October 24, 2003. Lilly anticipates submitting the final submission on September 30, 2003. The only and final submission will be the chemistry drug product information.

The clinical team sent facsimiles dated April 30, May 19, June 10, 19, 23, and 30, 2003 to Lilly requesting missing images and CT scan reports for the NDA.

MEETING OBJECTIVES:

Lilly requested a teleconference to understand the continuing request for further data regarding the mesothelioma responders.

DISCUSSION:

Dr. Nguyen requested a clarification of why FDA has several requests for missing imaging data or CT scan reports. Lilly explained that the imaging data has been digitized and that FDA had been supplied with data that would allow FDA to access the mesothelioma responders. Lilly is aware of the discrepancies between the investigator and independent reviewer's assessments. Lilly, in conjunction with a vendor, ——— , provided FDA with a computer system and laptop for Dr. White to be able to access assessments by the independent imaging reviewers' reports from the image database.

Dr. White indicated that he was not able to access the images from the laptop provided to him. Also, the set of CDs, containing the images, are in code and Dr. White does not know which CD has images for a particular patient visit. Lilly will follow-up with ——— representative, to ensure that Dr. White has the appropriate software to access the imaging data on the laptop.

Dr. White explained the reasons for his requests of the CT scan reports and for patient clarification of cases that had discrepancies in their response. Lilly indicated that it is resource intensive to obtain translated CT reports from non-English language countries. However, Lilly and FDA agreed that Lilly can provide CT scan reports for English language countries now. The CT scan reports from non-English language sites will follow.

Lilly will respond to FDA request for clarification regarding discrepancies or why scanswere not provided for various patients to the independent reviewers.

ACTION ITEMS:

1. Lilly will contact ——— representative, to discuss with the Dr. White's problems in access the scanned database from the laptop computer.
2. Lilly will provide CT scan reports to DODP for English language reports. To follow, Lilly will translate or provide to FDA the CT scan reports that have been completed in a language other than English.
3. Lilly will provide a list containing the patients that FDA requested for clarification on the response determination. This list will also provide a reason for the discrepancy or why certain scans were not provided to the independent reviewers and the FDA.

There were no unresolved issues. The meeting concluded at 12:00 p.m.

/S/

{See appended electronic signature page}

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

/S/

{See appended electronic signature page}

Robert White, Jr., M.D.
Medical Officer

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/s/

Robert White
7/31/03 05:41:00 PM

TELECONFERENCE

MEETING MINUTES

MEETING DATE: February 12, 2003 **TIME:** 11:30 a.m. **LOCATION:**WOC2/2064

NDA: 21-462 **Meeting Request Submission Date:** 2-27-03
Briefing Document Submission Date: none

DRUG: Alimta® (LY231514)

SPONSOR/APPLICANT: Eli Lilly & Company

TYPE of MEETING:

1. Statistical Guidance

2. **Proposed Indications:** Mesothelioma

FDA PARTICIPANTS:

Gang Chen, Ph.D.	--	Statistical Team Leader
Yong-Cheng, Wang, Ph.D.	--	Statistical Reviewer
Martin Cohen, M.D.	--	Clinical Team Leader
John Johnson, M.D.	--	Clinical Team Leader
Robert White, M.D.	--	Clinical Reviewer
Sheila Ryan, Pharm.D.	--	Project Manager
Patty Garvey, R.Ph.	--	Project Manager

INDUSTRY PARTICIPANTS:

James Symanowski, Ph.D.	--	Vice President, Therapeutic Area Head, Oncology
Binh Nguyen, M.D., Ph.D.	--	Medical Director, Alimta Product Team
John Worzalla	--	Regulatory Research Scientist, US Regulatory Affairs
incorrect → Gary Lewis, M.S. not present.	--	Associate Director, Regulatory Affairs

MEETING OBJECTIVES (from meeting request):

To discuss the FDA and Eli Lilly differences between log rank p-value calculations for the supplemented patients in study JMCH.

BACKGROUND:

1. December 3, 2002 Eli Lilly NDA 21-461 Alimta presentation to FDA
2. January 21, 2003 NDA 21-461: Meeting request with statistical review team

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

FDA stated that the p-value that they presented at the December 3rd meeting was unofficial. The p-value was calculated by the clinical team leader using the JMP software. However, the official statistical analyses will be done by the statistical review team during the NDA review process.

It was determined that the FDA and Lilly are using same method to calculate the p-value, therefore there should not be any discrepancy in the p-value calculation from the FDA or Lilly.

FDA also indicated that they have not completed their calculation.

ACTION ITEMS: None

There were no unresolved issues and the meeting concluded at 12:00 p.m.

{See appended electronic signature page}

/S/

Patty Garvey, R.PH.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

/S/

Yong-Cheng Wang, Ph.D.
Statistical Reviewer

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/s/

Yong-Cheng Wang
3/27/03 12:43:50 PM

TELECON MINUTES

MEETING DATE: 12/17/02 **TIME:** 1:00 **LOCATION:** WOC II Conf. Rm. A

IND: 40,061 SN 478 **IND Document Submission Date:** 12/2/02

DRUG: ALIMTA (LY231514 disodium) **INDICATION:** Malignant Mesothelioma

APPLICANT: Eli Lilly

TYPE of MEETING/TELECON: CMC Telecon

FDA PARTICIPANTS:

Rik Lostritto, Ph.D., Chemistry Team Leader, DODP
Chengyi Liang, Ph.D., Chemistry Reviewer, DODP
Paul Zimmerman for Dotti Pease, Project Manager, DODP

PARTICIPANTS:

Jeffrey Ferguson, Global Regulatory, CM&C
Doug Balogh, Ph.D., Alimta Dev. Proj. Man.
Larry Larew, Ph.D., Dir., Phar. Res. & Dev.
Dinesh Mishra, Ph.D., Res. Scientist, Pharm. Res.
Sheryl Peoples, Assoc. Sen. Pharma Chemist
Heather Weimer, Ph.D., Sen. Analytical Chemist
Diane Zezza, Ph.D., Dir., Regulatory CM&C

MEETING OBJECTIVES: Telecon to discuss Alimta CMC proposal dated 12-2-02

BACKGROUND: The NDA (21-462) is currently submitted as a rolling review with the clinical portion submitted. The CMC submission is planned for September 2003 which would complete the NDA. This proposal is for an alternate container closure system relative to the transfer of the manufacture of the drug product from Indianapolis to Fegersheim, France.

DISCUSSION and DECISIONS REACHED:

The proposed protocol and related changes are acceptable.

The applicant noted that they will submit [redacted] stability data with the drug product submission.

Regarding PAI, we noted that we will initiate the drug substance (DS) inspection when that section is submitted. All sites should be ready for inspection.

The applicant asked if we could initiate the drug product (DP) pre-approval inspection (PAI) before that section is submitted. After further discussion within the Agency, the applicant was notified that there is risk involved if the inspection request is made before the submission as the field will reject the request if the submission is not available. The most prudent course is to wait until the submission is made.

ACTION ITEMS:

Sponsor to submit CMC sections as agreed.

/S/ /S/

Paul Zimmerman for Dotti Pease
Project Manager

Concurrence Chair:
Rik Lostritto, Ph.D.
Chemistry Team Leader

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/s/

Dotti Pease
1/6/03 02:19:16 PM
CSO

Richard Lostritto
1/7/03 03:30:56 PM
CHEMIST

TELECON MEETING MINUTES

MEETING DATE: 5/15/02 TIME: 10:30 A.M. LOCATION: WOC II
Conf. Rm. B

IND: 40,061 SN 396

Telecon.....6/21/02 CMC telecon for pre-NDA
Fax.....7/30/01 CMC Issues
Telecon.....7/31/01 Discuss Clinical & CMC Safety
Meeting Request.....9/10/01 351
Meeting Request .....10/19/01 Serial Number 356
Briefing Document Submission.....10/19/01 Serial Number 359
Fax.....11/21/01
Telecon.....11/21/01 Discussion clarifying fax
Meeting Request.....2/15/02, Serial Number 385
Request to reschedule meeting .....3/26/02 Serial Number 396
Briefing Document Submission ....4/12/02, Serial Number 405

DRUG: Alimta **INDICATION:** Malignant Pleural Mesothelioma

APPLICANT: Eli Lilly

TYPE of MEETING/TELECON: CMC Telecon

FDA PARTICIPANTS:

Rik Lostritto, Chemistry Team Leader, HFD-810
Chengyi Liang,Ph.D., Chemistry Reviewer, HFD-810
Brian Booth, Ph.D., Biopharm Reviewer (participated in pre-meeting)
Debbie Vause, Project Manager, HFD-150

invitees

John Simmons, Ph.D., Deputy Dir., DNDC I , HFD-810
Hasmukh Patel, Ph.D., Dep. Dir., DNDC I, HFD-810
Richard Pazdur, M.D., Division Director, HFD-150
Grant Williams, M.D., Deputy Division Director, HFD-150
Donna Griebel, M.D., Team Leader, HFD-150
Robert White, M.D., Medical Reviewer, HFD-150
David Morse, Pharm/Tox Team Leader, HFD-150
Doo Young Lee Ham, Ph.D., Pharm/Tox Reviewer, HFD-150
Atiq Rahman,Ph.D., Biopharm Team Leader
Gang Chen, Ph.D., Statistical Team Leader
Dotti Pease, Project Manager, HFD-150

PARTICIPANTS:

Sally Anliker, Ph.D. Manager Regulatory CM&C
Doug Balogh, Ph.D. Development Project Manager
Jeff Ferguson, Regulatory Research Scientist (Regulatory CMC)

Larry Larew, Ph.D. Director, Pharmaceutical Research & Development
Dinesh Mishra, Ph.D. Research Scientist, Pharmaceutical Research
Heather Weimer, Ph.D. Senior Analytical Chemist
Doris Weisman, Ph.D. Research Scientist, Statistical / Math Sciences
John Worzalla Regulatory Research Scientist (US Regulatory- Clinical)
Diane Zezza, Ph.D. Director Regulatory CM&C

MEETING OBJECTIVES: Discuss proposed CMC development and adequacy of NDA submission.
Discuss rolling submission and CMC timeline

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Complete pre-clinical and clinical NDA sections complete except CMC Sections) Available 3Q02

2. Complete drug substance (DS) NDA section Available 4Q02 Need to explore timing of DS PAI

3. Drug product (DP) NDA section containing: Available April 03
   - Complete NDA Sections for Components, Composition (including formulation rationale), Inactive Ingredient Specifications and Methods, Manufacturing Facilities, Method of Manufacture, Container/Closure System, Methods Validation, and — Validation Package.
   - Batch Analysis results (release data) for supporting and the — primary stability batches (rate limiting data). Specification section listing all tests and methods. Acceptance criteria available for all tests except for stability indicating tests, which will be TBD pending additional primary stability data. Stability section containing supporting stability lot data without statistical analysis or a proposed shelf life.

4. Provide amendment to NDA containing: Available 3Q03
   - Updated supporting stability data and — primary stability data. Data analysis to support a proposed product shelf life.
   - Interim (wider) shelf life specifications for all stability indicating tests based on limited primary stability and the long term supporting stability studies. Provide a commitment to tighten interim specifications post approval as more data become available.
   - Executed Batch Records
   - Need to discuss timing of DP PAI

   FDAResponse: We have numbered your bulleted items as 1 through 4 above for convenience.

- Referring to items 3 and 4 above: To be useful for drug product shelf life determinations, supportive stability studies should utilize the same exact drug product formulation, identical to-be-marketed container closure system(s), the same ICH storage conditions, pilot scale or larger batches (DS and DP), identical tests and methods (DS and DP), identical specifications and data reporting methods (DS and DP), and the same stability protocols. Any differences from the to-be-marketed primary stability case(s) threaten to diminish or eliminate the applicability of supportive stability studies to a degree related to importance of those differences. In general, the more and earlier relevant primary stability data there are, the better for your case.

- When you update the primary stability data package as described in item 4 above, you should also update the supportive stability data as appropriate. Your proposed interim specifications should utilize the approaches put forth in the ICH Q6A Guidance for Industry. Please note that other criteria in addition to the primary stability batch performance need to be considered (e.g., overall manufacturing capability, supportive stability data, etc.).

- We note that your final submissions (item 4 above) are proposed to include executed batch records and discussion of PAI timing. It seems reasonable that you cannot conduct the activities cited in item 3 above without also completing executed batch records and also to be ready for a PAI. Therefore, why not submit these items along with those cited in item 3 above in April 03 to save time?

- The sooner the PAI request is submitted, the better. At this time, please provide the locations of all DS and DP, manufacturing, testing, packaging and labeling sites so we may provide you with further feedback regarding your proposed PAI timing plans. In general, when you are ready for a PAI you should submit the relevant data and CMC sections and not before. PAI delays resulting from the applicant's lack of readiness threaten a timely and favorable action on your NDA.

ACTION ITEMS:

1. The sponsor will supply a list of testing sites for DP and DS.

/S/

Debbie Vause, Project Manager

Concurrence Chair: /S/

Ric Lostritto, Ph.D.
CMC Team Leader

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/s/

Debra Vause
5/15/02 03:58:39 PM
CSO

Richard Lostritto
5/15/02 04:19:36 PM
CHEMIST

MEETING MINUTES

MEETING DATE: 6/21/01 TIME: 11:00 A.M. LOCATION: WOC II
Conf. Rm. B

IND: 40,061

DRUG: ALIMTA INDICATION: Treatment of mesothelioma

APPLICANT: Eli Lilly and Company

TYPE of MEETING/TELECON: CMC telecon for pre-NDA

FDA PARTICIPANTS:
Eric Duffy, Ph.D., Chemistry Team Leader
Debbie Vause, Project Manager, HFD-150

PARTICIPANTS: Jeff Ferguson, CMC, U.S. Regulatory Affairs

MEETING OBJECTIVES: Discuss CMC pre-NDA issues

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

SPONSOR'S QUESTIONS AND FDA RESPONSES

Sponsor: USAN name approved, Pemetrexed Disodium

FDA: Do not have to use disodium

Sponsor: Process change on drug substance side

FDA: There are 2 primary issues
- Impurity profile
-

Sponsor: Reduction on the antioxidant side of the drug product
Sponsor: lots
ACTION ITEMS: The sponsor will submit a request for waiver of the requirement for a bioequivalence study.

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/s/

Debra Vause
6/25/01 02:42:12 PM
CSO

Eric Duffy
6/26/01 12:46:06 PM
CHEMIST

TELECON MINUTES

MEETING DATE: June 21, 2000 TIME: 3:00 LOCATION: B

IND: 40,061 Meeting Request Submission Date: 3-8-00
Additional preparation documents: 4-13-00 submission and 6-9-00 fax

DRUG: MTA INDICATION: mesothelioma

SPONSOR/APPLICANT: Lilly

TYPE of TELECON: follow-up to EOP2 re: mesothelioma indication

FDA PARTICIPANTS: Richard Pazdur, M.D., Dir., HFD-150
John Johnson, M.D., Medical Team Leader, HFD-150
Robert White, M.D., Medical Officer, HFD-150
Dotti Pease, Project Manager, HFD-150

INDUSTRY PARTICIPANTS: Paolo Paoletti, M.D., MTA Project Team Leader
Gregory Brophy, Ph.D., Dir., NA Reg. Affairs, Cancer
John Worzalla, Sen. Reg. Representative

MEETING OBJECTIVES: Discuss three EOP2 Meetings (9-28-98; 6-25-99; and 3-1-00)

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Could the 2nd line NSCLC trial support the mesothelioma indication?

FDA – The mesothelioma indication could be supported by the second line lung cancer study However, we would request an additional lung cancer trial to support the second line lung cancer indication. .

2.

This would be discussed further in the pre-NDA meeting.

3. Would FDA accept an interim analysis on the mesothelioma trial?

FDA – The primary endpoint of this trial is survival. We strongly discourage the submission of the application based on interim analysis of secondary endpoints of response rate, time to progression or "symptom benefit" without mature survival data. Because of the poorly defined radiographic disease encountered in mesothelioma patients, endpoints of response rate and time-to-progression may be problematic and difficult to reproduce leading to a lack of credibility of these endpoints. In addition, the interpretation of the secondary endpoint of symptom benefit (which is a clinical endpoint) may be problematic from a regulatory viewpoint due to the lack of double blinding. The demonstration of an improved survival associated with MTA would provide the agency and, more importantly, the public with the confidence that MTA is an effective agent providing clinical benefit. Unfortunately, since mesothelioma patients have a rapid downhill course and short survival after progression of any therapy, survival data could be collected in a timely manner. Survival data would lead to a definitive conclusion regarding MTA's clinical benefit. If you insist on pursing a submission based on your secondary endpoints, the Division would like a pre-NDA meeting to discuss your findings.

/S/ 6-22-00
Dotti Pease, Project Manager

Concurrence Chair: /S/
Richard Pazdur, M.D.
Division Director

cc: ORIG. IND 40,061
Div. File
Attendees electronically
HFD-150/DWPease/ 6-22-00/rev. per RWhite, RPazdur, JJohnson 6-27-00

MEETING MINUTES

MEETING MINUTES

MEETING DATE: March 1, 2000 **TIME:** 10:30 AM **LOCATION:** Conf. Rm. "G"

IND: 40,061

Meeting Request Submission Date: January 25, 2000
Briefing Document Submission Date: February 16, 2000
Additional Submission Dates: None

DRUG: MTA (MultiTargeted Antifolate, LY231514)

SPONSOR/APPLICANT: Lilly Research Laboratories

TYPE of MEETING:

1. End of Phase 2 (2nd meeting)

2. Proposed Indication: For the use of MTA in patients with mesothelioma.

FDA PARTICIPANTS:

Richard Pazdur, M.D. - Director, Division of Oncology Drug Products
James Krook, M.D. - FDA ODAC Member – pre-meetin only
John Johnson, M.D. - Medical Team Leader
Robert White, M.D. - Medical Officer
David Smith, Ph.D. - Statistical Team Leader
Doo Young Lee-Ham, Ph.D - Pharmacology/Toxicology Reviewer
Eric Duffy, Ph.D. – Chemistry Team Leader
Alvis Dunson -Project Manager

INDUSTRY PARTICIPANTS:

Gregory Brophy, Ph.D. – Director, North American Regulatory Affairs, Cancer
Axel Hanauske, M.D. – Medical Director, MTA Product Team
Clet Niyikiza, Ph.D. - Research Scientist, Statistician
Paolo Paoletti, M.D. – MTA Product Team Leader
James Rusthoven, M.D. - Clinical Research Physician
Brian Stuglik - MTA Product Team, Chief Operating Officer
John Worzalla - Senior Regulatory Reprensative
—). – Consultant, —
— - Consultant, —

MEETING OBJECTIVES:

To discuss changes of vitamin supplementation instituted for the ongoing mesothelioma registration trial.

QUESTIONS for DISCUSSION with FDA RESPONSE, and DECISIONS REACED:

Question 1a. Does the FDA agree that toxicity and mortality data support a programmatic intervention to improve patient safety in LY231514 trials and that daily low dose folic acid supplementation appropriately serves this purpose?

FDA RESPONSE: The addition of vitamins to the pivotal trial(s) is at Lilly's risk. We share your concerns about toxicity; your options include:

1. [redacted]
2. [redacted]
3. Continue the current trial with the addition of vitamins and with a recalculated sample size to provide adequate power for comparisons.

- Lilly agrees to option #3.
- After approximately 150 patients are treated on the revised protocol with vitamin supplementation, a survival analyses will be done pooling the approximately 150 patients with vitamin supplementation with the approximately 150 patients without vitamin supplementation. Lilly will soon submit to FDA a prospective detailed plan for this analysis.

Question 1b. Does the FDA agree that a randomized trial comparing patients receiving LY231514 with and without vitamins is no longer feasible or advisable given the demonstrated toxicity risks to LY231514 patients?

FDA RESPONSE. See 1a.

Question 2. Do the proposed analyses of efficacy and safety described here for Study JMCH sufficiently address the impact of the folic acid supplementation intervention on the results of this trial such that the trial will qualify as a randomized, well-controlled trial for the mesothelioma and NSCLC indications?

FDA RESPONSE. We do not believe the proposed changes would allow us to adequately determine the benefit of adding vitamins to this trial. The proposed package for registering MTA is weakened by these changes. Tampering with the pivotal trials does not strengthen the case for well-controlled trials. There is no standard dose of vitamins administered to patients and we believe this is problematic. Please specify exact dose(s).

- Lilly will provide dosing information for each patient (i.e., patient diary, pill count).
- Lilly will provide a revised statistical plan before proceeding with this trial. Specifically, the plan should contain information with respect to interim analysis on survival, and the statistics tests proposed for analyzing vitamin supplementation. A Type I Error penalty is necessary if the trial should be stopped.

Question 3a. Does the agency support the replacement of vinorelbine with — as the comparator in the JMBQ study?

FDA RESPONSE. No. A new trial should be initiated and a new protocol should be submitted. Does the proposed sample size have sufficient power to demonstrate superiority of MTA over —? The trial is too small to demonstrate equivalence.

Question 3b. Does the agency agree that these modification will allow Study JMBQ to continue to serve the role of a randomized, well-controlled trial in support of the mesothelioma and second-line NSCLC indications, as previously discussed in the End-of Phase II meeting in June of 1999?

FDA RESPONSE. We remind you that two trials in NSCLC will be required to obtain this claim. In addition, your eligibility in the lung cancer trial should be similar to the taxotere trial in order to gain approval based on equivalence.

- Taxotere is an acceptable comparator.
- Taxol prior therapy is acceptable with stratification.
- Patients who progress on prior therapy will be acceptable in the labeling.
- —
- FDA will get back to sponsor on the number of trials in NSCLC and no commitment is made at this meeting.

ADDITIONAL COMMENTS.

1. Your proposed clinical benefit response is not acceptable. At a mininum, you must use the Agency's Clinical Benefit Response table listed below for the mesothelioma trial. This table is also listed in the meeting minutes dated June 25, 1999. Please note that clinical benefit response alone, as measured in this study, will not be a basis for approval.

CLINICAL BENEFIT RESPONSE

	Pancreas ca GEMZAR	Mesothelioma MTA	**FDA Recommendations for Mesothelioma trial**
change in pain intensity			
change in analgesic consumption			
change in performance status (Karnofsky)			
weight change		N/A	
Dyspnea			

2. More justification should be submitted than you have presently for the use of MTA + vitamins.

THE PROTOCOL—H3E-JMCH
2/14/99; serial #206

Revised Protocol Sections

page 3:

A rationale for the B12 injection has not been provided.

Protocol H3E-MC-JMCH (d)

Page 16: A rationale for the dose, timing, and schedule of administration of the vitamins has not been provided. What is the evidence that folate/B12 repletion will not stimulate tumor growth prior to the administration of chemotherapy?

Page 20: A creatinine clearance derived with urine collection and serum creatinine may achieve the goal of patient safety better than calculated creatinine clearance derived by formula and serum creatinine.

Page 30: Are leucovorin and thymidine rescue still necessary if vitamins are added to the protocol?

Page 38: In the Disease Status section, delete references to [redacted]

Page 51: Data Analysis Methods: there are no specifics for the evaluation of the impact of vitamins on efficacy endpoints.

Page 52: An intent-to-treat analysis should also be performed.

Page 54-56: Since the plan is to complete the accrual of patients to the pivotal trial, the rationale for the interim analysis is weak. Lilly may believe that evidence in their interim analysis may support early filing and stopping of the trial. The FDA is not convinced that clinical benefit response data will warrant early filing. The interim analysis for efficacy endpoints should be deleted. Alternatively, Lilly may accrue all the required patients and then perform an interim analysis of the first 75 patients per arm.

The meeting was concluded at 12:30 pm.

/S/ 4/5/00
Alvis Dunson, Project Manager
Minutes preparer

Concurrence Chair /S/ 4/5/2000
Robert White, M.D.
Medical Officer

MEETING ATTENDANCE

DATE: March 1, 2000 TIME: 10:30am PLACE: WOC2, 6th Flr, Rm G

IND: 40,061 Drug: MTA

SPONSOR: Eli Lilly and Company

SUBJECT: To discuss recent changes in the ongoing mesothelioma registration trial.

Printed Name	Signature	Organization
Alice Dawson		FDA-150
David Smith		HFD-710 FLA
R PAZDUR		FDA
JOHN JOHNSON		FDA
Doo Y Lee Hans		FDA
Robert White		FDA
Eric Duffy		FDA
Greg Beaphy		Eli Lilly
CLET NIYIKIZA		Eli Lilly.
PAOLO PAOLETTI	Paolo Paoletti	Eli Lilly
Theresa Kusthaven		Eli Lilly
AXEL-R. HANAUSKE		ELI LILLY
BRIAN STUGLIK		Eli Lilly
JOHN WORZALLA		Eli Lilly

cc:
Original IND 40,061
HFD-150/Div File
/RWhite
/ADunson

cc electronically only:
RPazdur
JJohnson
GChen
ADunson
DPease
LVaccari

F/T: ADunson/4.5.00 /mydocs/dodp/lilly/40061/minutes/030100eop2

MEETING MINUTES

MEETING MINUTES

MEETING DATE: June 25, 1999 **TIME:** 11:00 AM **LOCATION:** Conf. Rm. "G"

IND: 40,061

Meeting Request Submission Date: April 29, 1999
Briefing Document Submission Date: June 10, 1999
Additional Submission Dates: None

DRUG: MTA (MultiTargeted Antifolate, LY231514)

SPONSOR/APPLICANT: Lilly Research Laboratories

TYPE of MEETING:

1. End of Phase 2

2. Proposed Indication: For the use of MTA in patients with mesothelioma.

FDA PARTICIPANTS:

Robert Justice, M.D. -Acting Director, Division of Oncology Drug Products
John Johnson, M.D. - Medical Team Leader
Robert White, M.D. -Medical Officer
Gang Chen, Ph.D. -Statistical Team Leader
Alvis Dunson -Project Manager

FDA PARTICIPANTS (Pre-Meeting Only):

Robert Temple, M.D. -Director, Office of Drug Evaluation I
Rachel Behrman, M.D. – Deputy Director, Office of Drug Evaluation I
James Krook, M.D. - FDA Oncologic Drugs Advisory Committee(ODAC) Member
David Smith, Ph.D. – Statistical Reviewer

INDUSTRY PARTICIPANTS:

Gregory Brophy, Ph.D. – Director, North American Regulatory Affairs, Cancer
Astra Liepa, Pharm.D. – Health Outcomes Associate
Clet Niyikiza, Ph.D. - Research Scientist, Statistician
Paolo Paoletti, M.D. – MTA Product Team Leader
James Rusthoven, M.D. - Clinical Research Physician
Brian Stuglik - MTA Product Team, Chief Operating Officer
John Worzalla - Senior Regulatory Reprensative
—— – Consultant, ——

MEETING OBJECTIVES:

To discuss the clinical development of MTA for patients with mesothelioma.

PREAMBLE

This meeting package asks the same questions that were discussed at our meeting of September 25, 1998. The package did not provide persuasive arguments that would change the answers given at that meeting.

Survival is the primary endpoint for approval in mesothelioma. Superior survival of the MTA should be the basis for approval.

In mesothelioma, response rate is not a surrogate for survival or patient benefit and cannot be measured adequately. Serial measurements of disease is difficult and inaccurate in mesothelioma. It is uncertain that unidimensional disease measurements in mesothelioma will provide sufficient information for determining response rate (see discussion below). Approval based on response rate is unlikely.

Time to progression is not a sufficient surrogate for clinical benefit in mesothelioma. Like response rate, TTP cannot be measured adequately. Since the interval between disease progression and death is short (i.e., median 5 weeks [Byrne et al. Proc of ASCO. 1998;17:464a]), the primary endpoint should remain survival.

What happened to the randomized trial of MTA versus vinorelbine in NSCLC that was supposed to support the mesothelioma indication? We remind you of our agreement that the randomized control trial in NSCLC is essential to support the single randomized control trial in mesothelioma.

QUESTIONS for DISCUSSION with FDA RESPONSE, and DECISIONS REACED:

Question 1:

Would a submission on positive data in one or more of these endpoints be acceptable for "accelerated approval" in mesothelioma? The final survival results would be submitted for the "full approval."

Answer 1:

No.

Survival is the primary endpoint for approval in mesothelioma. Response rate and TTP are not surrogates for survival or clinical benefit in mesothelioma. These endpoints cannot be adequately measured. With a single, randomized study, clinical benefit with trending survival data may be sufficient for approval.

FDA is still concerned about the ability to assess response adequately in mesothelioma. However, if responses can be convincingly demonstrated and there are clinically relevant and statistically significant differences for all three endpoints (response rate, time-to-progression, and clinical benefit), the results would be sufficient for accelerated approval.

FDA cannot address other scenarios without seeing the data.

LILLY is committed to completing a 280-patient trial even if results are positive at interim analysis.

QUESTION 2:

If accelerated approval is not appropriate, can the NDA be submitted based on interim analysis of the Phase 3 registration study on the endpoints listed above (along with final results from the completed Phase 2 study) followed by submission of the mature survival results?

ANSWER 2:

See response to Question 1. The issue of the completed Phase 2 study will be addressed below.

Full survival data and analyses must be submitted with the NDA. A rolling submission is permissible under Fast Track but the review clock does not start until the submission is complete.

ISSUE 1:

Does this recent publication ("Measuring Response in Solid Tumors: Unidimensional Versus Bidimensional Measurement" by K. James et al., J. National Cancer Inst., 91:523-528, 1999) and the accumulating scientific data on the validity of unidimensional tumor measurements provide additional scientific support to DODP that unidimensional disease measurements will provide sufficient information for determining response rate in mesothelioma?

AGENCY RESPONSE:

Refer to response to Question 1.

ISSUE 2:

Do these proposals adequately address DODP's concern regarding validation and separate assessment of the proposed clinical benefit endpoint?

AGENCY RESPONSE:

No.

The proposed composite clinical benefit endpoint is not validated. The FDA will give more weight to separate assessment of each component of the proposed composite clinical benefit endpoint. If clinical benefit is to suffice for approval, double-blinding is strongly advised. Please submit your statistical plan.

Lilly will reconsider their clinical benefit criteria and submit a written proposal.

ISSUE 3:

The March 8, 1999 communication to Lilly from DODP "strongly urges Lilly to ——— ". We seek clarification as to this and ask if this signifies a shift away from the DODP opinion reported in the minutes of the End of Phase 2 meeting on September 25, 1998: "Mesothelioma is a rare disease. Depending on the quality of the mesothelioma trial design and data, further discussion may convince the Agency to accept one mesothelioma study and confirmatory evidence froma closely related disease, i.e., NSCLC."

AGENCY RESPONSE:

It does not signify any change as initially indicated.

ISSUE 4:

Would positive evidence of clinical efficacy (e.g., time to progression, clinical benefit, and/or response rate) at interim analysis for the Phase 3 registration study, together with data from the completed Phase 2 study of single agent MTA be sufficient for submission to seek a claim of MTA plus cisplatin for the treatment of malignant pleural mesothelioma?

Lilly seeks clarification of what is meant by "full approval of MTA" in DODP's statement above from their March 8 communication to Lilly.

AGENCY RESPONSE:

See response to Question 1.

Phase 2 trials in mesothelioma would be supportive if responses can be convincingly demonstrated.

Lilly agrees to submit the NSCLC trial data when completed.

ADDITIONAL COMMENTS
ABOUT
THE REGISTRATION TRIAL

1. There are extensive Sponsor comments to the Medical Officer review of this trial. There are no comments about the statistical review for this trial. These require comment and revisions of the protocol.

2. CLINICAL BENEFIT RESPONSE

	Pancreas ca GEMZAR	Mesothelioma MTA	**FDA Recommendations for Mesothelioma trial**
change in pain intensity			
change in analgesic consumption			
change in performance status (Karnofsky)			
weight change		N/A	
dyspnea			

3. Please indicate in the protocol how the patient's baseline analgesic consumption will be defined as "stable".

4. In the inclusion criteria, use the ECOG/Zubrod performance scale instead of the Karnofsky scale. Also, specify in the inclusion criteria, the performance status level acceptable for eligibility to the study.

5. Please clarify and indicate in the protocol (Section 3.6.1.3) the reason for administration of dexamethasone the day before, the day of, and the day after drug administration.

6. The protocol does not indicate how the lung cancer symptom scale, pulmonary function test, and lung density by CT scan data will contribute to the assessment of efficacy. In view of the proposed, single-blind design, data generated from the lung cancer symptom scale will be problematic since the investigator will know the patient's treatment arm and will be rendering the instrument.

7. In view that clinical benefit in mesothelioma has not been shown to correlate with survival, accrual to the study and survival follow up should be continued regardless of positive results from the interim analysis. Failure to complete the accrual to the study will jeopardize the study's power to detect a survival difference.

The meeting was concluded at 1:00 pm. There were no unresolved issues.

/S/ 7/23/99

Alvis Dunson, Project Manager
Minutes preparer

Concurrence Chair: /S/ 7/23/99

Robert White, M.D.
Medical Officer

cc:
Original IND 40,061
HFD-150/Div File
/RWhite
/ADunson

cc electronically only:
RJustice
JJohnson
GChen
ADunson
DPease
LVaccari

F/T: ADunson/7.23.99/mydocs/dodp/lilly/40061/minutes/62599eop2

MEETING MINUTES

ONCOLOGY DIVISION MEETING MINUTES

MEETING DATE: Sept. 25, 1998 TIME: 1:00 p.m. LOCATION: Conf. I, rm 6039

IND/NDA: IND 40,061
DRUG: LY 231514 (MTA)
SPONSOR: Eli Lilly & Co.

TYPE of MEETING:
1. End of Phase 2 – for clinical issues
2. Proposed Indication:

[ ]

FDA PARTICIPANTS: Oncology Division, HFD-150
Rachel Behrman, Deputy Office Director, ODEI
Robert Justice, Oncology Division Director
Julie Beitz, Deputy Division Director
John Johnson, Medical Team Leader
Robert White, Medical Reviewer
Liang Zhou, Chemistry Team Leader
Gang Chen, Statistics Team Leader
Linda McCollum, CSO

INDUSTRY PARTICIPANTS:
Gregory Brophy, Director, US Regulatory Affairs
Steven Hamburger, Regulatory Research Scientist, Cancer
Robert Johnson,
Astra Liepa, Health Outcomes Associate
Clet Niyikiza, Research Scientist, Statistician
David Seitz, Medical Advisor
Gerald Thompson, MTA Product Team Leader
Jackie Walling Director of Science and Operations for MTA Product Team
John Worzalla, Senior Regulatory Representative, Cancer

MEETING OBJECTIVES:
1. Discuss the issues surrounding the dose and dosing schedule for studies in patients with pleural mesothelioma and NSCLC who have failed prior platin-and taxane-based therapy.
2. Discuss the company's specific strategy for clinical and non-clinical development.
3. Identify and perhaps resolve issues that could alter the timing or quality of the NDA.

QUESTIONS for DISCUSSION, FDA RESPONSE and DECISIONS REACHED:

1. DOSE and SCHEDULE – Do you agree with the proposed dosing schedule for single agent MTA studies – specifically the registration studies involving NSCLC?

   A. Our agreement is limited to the proposed dosing schedule for single agent MTA. There does not appear to be sufficient efficacy advantage with the 600 mg/m^2 dose of MTA over the 500 mg/m^2 dose. Also, there is a trend for hematologic toxicity to be greater for the 600 mg/m^2 dose of MTA than for the 500 mg/m^2 dose. Therefore, the 500 mg/m^2 dose is recommended unless a dose response for overall response has been shown. Alternatively, patients can start at 500 mg/m^2 and the dose can be escalated to 600 mg/m^2 if tolerated.

   B. Our recommendation to use 500 mg/m^2 is advice and not a requirement.

2. MTA in Mesothelioma – The indication being pursued is: '

FDA preliminary comment: Usually, lead indications are approved with two studies. Mesothelioma is a rare disease. Depending on the quality of the mesothelioma trial design and data, further discussions may convince the Agency to accept one mesothelioma study and confirmatory evidence from a closely related disease, i.e., NSCLC.

   2a. Do you agree this is an acceptable registration strategy (i.e., patient population, patient numbers, endpoints) for accelerated approval for this indication?

      A. NO. Serial measurements of disease are difficult and inaccurate in mesothelioma. Confirmation of responses by FDA is likely to be impossible and the clinical benefit of response in mesothelioma is uncertain.

      Lilly has access to the technology ( ), the protocols and a dedicated assessment team in place to uniformly assess response in mesothelioma.

      B. Accelerated approval based on response rate is unlikely. In order to gain accelerated approval with the combination of MTA+cisplatin, you would have to provide evidence that MTA+cisplatin is better than any other combination in response and response duration.

We recommend that appropriately designed trials demonstrating clinical benefit, i.e. pain reduction, shortness of breath, etc. – see C & D, be used in a strategy for gaining full approval if survival benefit cannot be shown, instead of using response rate for accelerated approval, see prior FDA comments.

C. Survival should be the primary endpoint. Since survival is short in this population it should not take long to reach the endpoint which should be determinable with greater than 75% of your study patients dead.

D. Tumor-related symptoms could also be assessed in a blinded trial; this would make the results more convincing.

2b. Is the design of the study (JMCH) adequate and well controlled?

A. Yes, with reservations. This would be a better study if it were blinded.

B. A randomized trial of MTA+cisplatin vs. cisplatin alone is an adequate trial. However, the addition of the vitamins to the MTA arm without data that efficacy is not reduced is risky. We would like to know the basis for your determination that the addition of vitamins will not affect efficacy.

C. Lilly accepted these items as written.

2c. Do you agree that the choice of primary and secondary endpoints, and the analysis plan in study JMCH is acceptable?

A. NO. Response rate is not an acceptable primary endpoint in this disease. Survival should be the primary endpoint and superior survival in the patients on the MTA arm should be the basis for approval.

B. Secondary endpoints of response rate, duration of response and time to progression could be supportive of the primary endpoint.

C. Lilly accepted these items as written.

2d. Do you agree that allowing the measurement of unidimensional disease will provide sufficient information for determining response rate?

A. NO. It is uncertain that unidimensional disease measurements in mesothelioma will provide sufficient information for determining response rate.

B. Lilly accepted this item as written.

2e. Do you agree that there will be sufficient safety data to support registration, i.e., the studies of MTA and cisplatin in NSCLC may be used to support the safety profile obtained in mesothelioma?

A. YES. Accepted.

3. NSCLC – The indication being pursued is:

3a. Do you agree this is an acceptable registration strategy (i.e., patient population, patient numbers, endpoints) for this indication?

A. NO. Time to progression is not a sufficient surrogate for clinical benefit in NSCLC. Since the interval between disease progression and death is short, the primary endpoint should be survival.

Lilly agrees that survival will be the primary endpoint with time to progression as the secondary endpoint.

B. Two randomized, controlled trials will be needed. FDA is willing to discuss, in a pre-NDA meeting, the possibility of using only one randomized controlled trial in NSCLC with supportive data from a similar population instead of a second trial. We will need to see the data from all the trials. Be prepared to support your position with data.

3b. Is the design of the study (JMBQ) adequate and well controlled?

A. Yes, with reservations. A randomized trial of MTA vs. vinorelbine is an adequate trial; at least 75% of the patients randomized should have Stage IV disease. However, the addition of the vitamins to the MTA arm without data that efficacy in not reduced is risky.

B. Lilly accepted this item as written.

3c. Do you agree that the Thall-Simon-Ellenberg design is adequate to select the best MTA regimen in the Phase 2 portion of JMBQ (Thal, et al., 1998)?

A. NO. Please clarify what you propose. Will the best MTA regimen be selected based on efficacy, toxicity, or both?

B. Lilly plans to select the best MTA on toxicity only. All MTA patients will be included in the final analyses.

3d Do you agree with the choice of the primary and secondary endpoints as well as the statistical analysis plan and methods for the Phase 2 and Phase 3 portions of study JMBQ?

A. NO. All patients should be included in the MTA arm to minimize the need for correction in the final analysis.

B. Time to progression is not a sufficient surrogate for clinical benefit in NSCLC. Since the interval between disease progression and death is short, the primary endpoint should be survival.

C. Lilly accepted these items as written.

3e. Do you agree with our choice of quality of life instrument, symptoms, and analysis plan?

A. Since survival will be the primary endpoint, the contribution of QOL to the basis for approval is uncertain. We are willing to revisit this question at the pre-NDA stage, but suggest that pre-specified groups of symptoms be selected to study. Statistics will provide a written list of comments specific to the planned studies.

ACTION ITEMS: NONE

The meeting was concluded at 2:30p.m. There were no unresolved issues or discussion points.

/S/ 11.18.98
Linda McCollum, CSO
Project Manager

Concurrence: /S/ 11/19/98
Robert White, M.D.
Meeting Chair

cc:
Original IND/NDA:
HFD-150/ Div. File
HFD-150/ White, Johnson, LeeHam, Andrews, Liang, Zhou, Chen, Rahman, Pease
HFD-150/CSO-McCollum/ rd 092598/102698/111898

rd init. by: MO- White/102698
MTL- Johnson/102798

MEETING MINUTES
doc. id. 40061 clin eop2.998

MEETING MINUTES

MEETING DATE: 1-30-02 **TIME:** 10:30 A.M. **LOCATION:** Conference Room I

IND 40,061 Request Submission Date: 11/15/01
Briefing Document Submission Date: 12/20/01

DRUG: LY231514 Disodium (ALIMTA) (MTA)

SPONSOR/APPLICANT: Eli Lilly and Company

TYPE of MEETING:

1. Pre-NDA Meeting

2. **Proposed Indication:** [redacted]

FDA PARTICIPANTS:

Richard Pazdur, M.D., Dir., HFD-150
John Johnson, M.D., Medical Team Leader, HFD-150
Robert White, M.D., Medical Officer, HFD-150
Chengyi Liang, Ph.D., Chemistry Reviewer, HFD-150
David Morse, Ph.D., Pharm/Tox Team Leader
Doo Young Lee-Ham, Ph.D., Pharm/Tox Reviewer, HFD-150
Gang Chen, Ph.D., Stastical Team Leader, HFD-150
Brian Booth, Ph.D., Biopharm Reviewer, HFD-150
Gani Chico, M.D., Medical Officer, HFD-150
Lilia Talarico, M.D., Acting Assoc. Director, HFD-150
C. Michael Staschen, Ph.D., Biopharmaceutic Reviewer, HFD-150
Debra Vause, Project Manager, HFD-150

INDUSTRY PARTICIPANTS:

Paolo Paoletti, MD, Team Leader
Binh Nguyen, MD, PhD, Medical Director
James Rusthoven, MD, Medical Advisor
Clet Niyikiza, PhD, Oncology Research Advisor and Statistician
James Symanowski, PhD, Senior Research Scientist – Statistician
Robert D. Johnson, PhD, Senior Pharmacokineticist
Brian Stuglik, RPh, Director, Business Operations
Larry Larew, PhD, Director, Pharmaceutical Research and Development
Jeffrey Ferguson, Regulatory Research Scientist, Regulatory Affairs CMC
Steven T. Ward, Manager (Experience with Lilly's Recent Electronic NDA submissions to CDER)
Elizabeth Sloan, PharmD, Director
John Worzalla, Regulatory Research Scientist

MEETING OBJECTIVES: Discuss pre-NDA sponsor questions and FDA responses.

BACKGROUND:

A telecon on June 21, 2000 discussed 3 EOP2 meetings for mesothelioma held on 9/25/98, 6/25/99, and 3/1/00. The EOP2 meeting on March 1, 2000 was held to resolve and agree on the

implications of adding vitamins to the pivitol registration trial and for the supporting trials. In June 1999 an EOP2 meeting was held to discuss the mesothelioma indication. On December 3, 1998 a telecon occurred in follow-up to the 9/28/98 EOP2 meeting. The sponsor wanted to discuss the design of study H3E-MC-JMCH and how the study should be blinded.

March 20, 2001 a special protocol assessment was submitted by the sponsor for "A randomized phase 2 trial comparing ALIMTA plus best supportive care versus best supportive care alone in previously treated patient with locally advanced of metastatic malignant pleural mesothelioma".

This meeting was scheduled to discuss the submission of the NDA including labeling issues, statistical analysis, presentation of safety data, formatting of the NDA, financial disclosure, electronic submission, and other specific questions. The mesothelioma trials will include:

Phase 2 single agent trial of MTA (64 pts; 41 received vitamins)
Phase 1 MTA + cisplatin
Phase 1 MTA + carboplatin
Phase 3 RCT Cisplatin with or without MTA

Orphan drug status was granted by the FDA in 2001.

On January 23, 2001 the sponsor requested trademark review for ALIMTA for malignant pleural mesothelioma (serial number 288). The trademark request is still under review in OPDRA.

A separate pre-NDA meeting for chemistry, manufacturing and control is scheduled. A meeting request by the sponsor for a discussion of the results of their data safety monitoring review board results will be made soon. On March 27, 2002 a meeting to discuss instrument validation for the measurement of gene expression has been scheduled.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Does the FDA have any initial comments on the proposed indication statement, and does the FDA feel it is a reasonable and supportable proposal, understanding that FDA review of the data may result in additional comments?

FDA Response:

- Yes.

The wording should be:

This is the only statement that could possibly be supported sufficiently by your available data.

2. Does the FDA agree with the final Statistical Analysis Plan as defined in Section 6.4.4 of the briefing document?

FDA Response:

•The sponsor's final analysis plan is acceptable for this protocol.

3. Does the FDA agree to the presentation of safety data (groupings) for the ISS as outlined above and in Section 6.4.8 of the briefing document?

FDA Response:

- Yes, except the MTA + cisplatin safety analyses should have both combined (supplemented + nonsupplemented patients) and separate safety analyses (supplemented only; nonsupplemented only). (Refers to the pivotal study.)

4. Does the FDA agree with Lilly's proposed format and content of the NDA for LY231514?

FDA Response:

- Yes, except for the content. First, whether one randomized controlled trial using MTA in combination with cisplatin (JMCH) and one single arm trial using MTA as a single agent will be adequate for filing is dependent on the results of the trials. Unless the single RCT has a highly clinically and statistically favorable survival outcome, one RCT will not be sufficient. The FDA has previously indicated that a positive randomized controlled in 2nd-line NSCLC may be necessary to support the mesothelioma randomized controlled trial. Second, section 6.4.2 describes studies JMAP and JMBZ as "CRITICAL". These were not included in the DRAFT Table of Contents for the NDA, Item 8-Clinical Efficacy and Safety section.

- See Guidance--Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products--for quality of results from a single trial to provide evidence of effectiveness.

- Previously, the FDA has stated that serial measurements of disease are difficult and inaccurate in mesothelioma; confirmation of response

is likely to be impossible. Response rate is not an acceptable primary endpoint in this disease.

5a. Based on the information provided in the nonclinical pharmacology section (refer to Section 6.1), does the FDA agree that this is an acceptable nonclinical pharmacology package for the anticipated LY231514 MPM NDA?

FDA Response:

- Yes, the non-clinical studies are in order and acceptable for the NDA.

5b. Based on the information provided in the general pharmacology, toxicology, and ADME sections (refer to Section 6.1), does the FDA agree that this is an acceptable general pharmacology/toxicology/ADME package for the anticipated LY231514 MPM NDA?

FDA Response:

- The response is the same as 5a.

5c. Based on the information provided in the human PK section (refer to Section 6.3) does the FDA agree that this is an acceptable human PK package for the anticipated LY231514 MPM NDA?

FDA Response:

- Please include the preclinical metabolism/in vitro P-450 studies in the Human PK section as well.

6a. Does the FDA have any specific requests regarding the proposed electronic submission?

FDA Response:

- A Dictionary should be provided for the Electronic Database including a definition for all Table Names, Column Names, Row Names and field codes.

- In addition an Annotated Case Report Form should be provided with the corresponding Database name in each field on the Case Report Form.

6b. In accordance with the above-mentioned FDA guidance document, a paper review copy will only be submitted for the portions of the NDA listed below. Does the Agency concur?

- Item 4 – CMC documentation including the methods validation reports.

- Item 5 – Nonclinical pharmacology and toxicology summaries and study reports with the exception of individual animal data listings.

- Items 6, 8, and 10 – Summaries, ISS, ISE, and all full or abbreviated study reports, including the Appendices 16.1.1 and 16.1.2 as defined by the ICH E3 Structure and Content of Clinical Study Reports (July 1996).

- Lilly proposes to provide copies of publications in electronic format only.

FDA Response:

- This is acceptable.

6c. Laboratory datasets may be larger than 25 megabytes in size, but they will be broken into multiple 25 megabyte files to meet the requirements of the electronic submissions guidance. To aid in the review, are there particular laboratory variables that the FDA would like to see grouped in smaller archivable datasets?

FDA Response:

- Please provide whatever grouping Lilly believes is most useful.

7. Lilly is willing to make arrangements with the vendor to provide for an electronic reader capability at the FDA. Is the FDA interested in this electronic capability?

FDA Response:

- Please provide further information at the Pre-NDA meeting.
- The sponsor will consider providing images for responders at baseline and at best response.

8. Does the DODP agree with Lilly's proposal to only provide financial disclosure information for the studies listed above (JMCH and JMDR) in the anticipated LY231514 NDA?

FDA Response:

- What criteria did Lilly use to determine the studies for which Financial Disclosure will be provided?

- Financial Disclosure must be provided for all studies not completed by Feb. 2,
1998.

- Eli Lilly will provide Financial Disclosure for the 7 studies described in the briefing document.

9. Lilly seeks DODP input regarding outstanding issues from previous End of Phase 2 Meetings and Teleconferences as described in Sections 3.1.1. to 3.1.5. of the Briefing Document.

FDA Response:

- No question submitted.

10. Finally Lilly seeks DODP input regarding Open Business issues as described in Sections 3.3.1. to 3.3.4. of the Briefing Document. In particular, Lilly seeks clarification on the following issue in Section 3.3.1.

- Please clarify if DODP is requesting (in FDA's 14 December 2001 communication to Lilly) CRFs for all SAE Drug and Non-Drug Related events for the LY231514 plus cisplatin or carboplatin trials (JMCH, JMAP, JMAU, JMAY, JMBZ) as well as the LY231514 supportive single-agent trial (JMDR).

FDA Response:

- That is correct.

ADDITIONAL FDA COMMENTS:

Financial Disclosure Final Rule:

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety.
Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

Pediatric Exclusivity:

Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if this drug is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Requirement (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act" at Drug Information Branch (301) 827-4573 or http://www.fda.gov/cder/guidance/index.htm. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at http://www.fda.gov/cder/guidance/3756dft.htm.

Pediatric Final Rule:

Please note that you have been granted Orphan Drug status on August 28, 2001 therefore the Pediatric Final Rule (63 FR 66632) does not apply.

NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

DIVISION OF SCIENTIFIC INVESTIGATIONS REQUESTS:

List of additional site-specific data DSI will need from the sponsor after DSI has determined the sites ((U.S. and/or foreign) for inspection

The sponsor is requested to provide the following for **each site selected for inspection:**

- Address and phone number of the site
- Investigator's 1572
- List of investigator(s) and sub-investigators on 1572, and their c.v.
- Protocol and amendments approved for the site

- Sample blank CRF and case report data tabulations for the site with coding key
- Copies of completed CRFs of all (or selected number of) subjects enrolled
- Randomization list for the site
- Total number of subjects entered in each study arm
- The number of drop outs/discontinued subjects, identified by the subjects' study numbers for the site, together with the reasons for each dropout/discontinuation
- List by the subject's study numbers all evaluable / inevaluable subjects
- List by the subject's study numbers all reportable AEs, SAEs and deaths with a narrative for all SAEs and deaths
- List of protocol violations and protocol deviations for the site
- Results (by site) of the "critical" primary efficacy parameters (with descriptive statistics: mean, SD, median, range at baseline and at endpoint, or change from baseline at endpoint, etc., or if the endpoint is non-parametric, number of deaths, number of responders, etc.)
- Data listing of the efficacy endpoint data for each subject for each of the centers
- IRB names (and SOPs)
- Names of monitors and monitoring logs

Additional information required for foreign sites selected for inspection

- Name, phone number, fax number and address of contact person from the sponsor
- List of hotels near the site(s) to be inspected, room rates, etc.
- Written confirmation by the sponsor of the dates of inspection including names of FDA personnel involved.
- Written assurance from the sponsor (i.e., sponsor's authorized representative within the US) of free access to the records, right to make copies of needed documents.
- Availability of Xerox machine in the inspection workroom or in immediate vicinity for our unrestricted use.
- Sponsor provides a translator who is not affiliated with the sponsor or the study and is acceptable to FDA
- Additional equipment as needed for the inspection (i.e., X-ray viewer in the room, microscope to evaluate slides, etc.)

- Someone representing the sponsor should be at site to delete subject identifiers from copied documents (i.e., names, hospital number, etc.)
- The local equivalent to the PDR should be available in the workroom for FDA use during the inspection.

- A list of subjects' names, study numbers, hospital identifiers, and drug treatment groups should be available for FDA use during the inspection. This list will remain in the (secure) inspection workroom, must not be copied, and must be returned to the clinical investigator at the conclusion of the inspection (important to protect confidentiality).

- All source documents (including hospital charts, laboratory reports, biopsy reports, X-rays, ECGs, ultrasonograms, CT scans and reports, biopsy slides, etc.) for the study should be available in the workroom for FDA review for the duration of the inspection.
- All CRFs, consent forms, IRB approvals, pharmacy records, drug accountability records, and correspondences related to the study should be available in the workroom for FDA review for the duration of the inspection.

ACTION ITEMS: (Include description, identify person responsible and due date.)

1. Lilly will provide the rationale for use of ALIMTA single agent and ALIMTA plus carboplatin in the protocol for treatment.

2. Lilly will request a telecon or meeting to discuss pivotal trial filability issues.

3. Lilly will discuss Additional FDA Comments if there are any issues.

4. The Project Manager will follow up with OPDRA regarding progress of review for ALIMTA.

The meeting concluded at 11:25 A.M. There were no unresolved issues or discussion points.

Original IND 40,061
HFD-150/Div File

MEETING MINUTES

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/s/

Robert White
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INTERNAL MEETING MINUTES

MEETING DATE: November 13, 2003 **TIME:** 9:00 am **LOCATION:** WOC2/rm 2064

NDA: 21-462 **Meeting Request Submission Date:** N/A
Briefing Document Submission Date: N/A

DRUG: Alimta® (pemetrexed, LY231514)

SPONSOR/APPLICANT: Eli Lilly & Company

TYPE of MEETING:

1. Pre-Approval Safety Conference

2. **Proposed Indications:**
   Alimta® in combination with cisplatin for the treatment of malignant pleural mesothelioma.

FDA PARTICIPANTS:

Richard Pazdur, M.D.	--	Director, Division of Oncology Drug Products (DODP)
John Johnson, M.D.	--	Medical Team Leader
Robert White, Jr., M.D.	--	Medical Reviewer
Doo Y. Lee Ham, Ph.D.	--	Pharmacology/Toxicology Reviewer
Brian Booth, Ph.D.	--	Clinical Pharmacology & Biopharmaceutics Reviewer
Kate Phelan, R.Ph.	--	Safety Evaluator, Office of Drug Safety (ODS)
Robert Kang, Pharm.D.	--	Project Manager, ODS
Patty Garvey, R.Ph.	--	Project Manager

MEETING OBJECTIVES:

To identify potential expected adverse events that the Office of Drug Safety should be aware of for post-marketing surveillance.

DISCUSSION:

Ms. Phelan asked whether the addition of folate and vitamin B_{12} has been shown to decrease the toxicity of Alimta. Dr. White indicated that it appears to lessen the toxic effect of Alimta.

Ms. Phelan asked for clarification of the definition for toxic death. Dr. Pazdur indicated that this mean death due to toxicity.

Ms. Phelan asked if there are any particular adverse events that should be monitored in post-marketing period. Dr. White replied "No". There is no indication from the clinical data submitted in the NDA that there is any new or unusual adverse events unfamiliar to practicing oncologists.

The meeting concluded at 9:15 am.

/S/ *[See appended electronic signature page]*

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

/S/ *[See appended electronic signature page]*

Robert White, Jr., M.D.
Medical Officer

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/s/

Robert White
11/19/03 03:36:16 PM

Center for Biologics Evaluation and Research (CBER)

Imaging Review of NDA

Date: September 23, 2003

From: George Mills, M.D.

To: Robert White Jr., M.D.

cc: Patricia Garvey

Subject:

Imaging Review of the NDA 21-462 Independent Review of CT Scans to Assess Mesothelioma Tumor Response to the Investigational Agent, Alimta

Oncology Indication: Treatment of Mesothelioma

Investigational Agent: Alimta

Sponsor: Eli Lilly

CRO: [redacted]

Consult Summary with Regulatory Recommendations:

I have completed the imaging review of the independent review of CT scans utilized for the monitoring of Mesothelioma tumor response to Alimta in NDA 21-462.

Based on this imaging review and the associated database audit, I have the following regulatory comments and recommendations:

- There are 47 subjects, which demonstrate a confirmed overall objective response, as assessed by the independent review panel and confirmed by my review, (see **Attachment B** for full listing with observations and comments).

- In the assessment of subjects listed and reported in the NDA 21-462 as overall objective responders, 22 subjects are reported as overall objective responders but were found to be non-responders by the independent review. My review confirmed 21 of these 22 subjects as non-responders (see **Attachment A** for full listing) and one subject qualifies as an overall objective responder based on the tumor measurements. This inconsistency of response assessments between the NDA dataset and the independent review dataset suggests that the response assessments reported in NDA 21-462 are not based on the independent review. The sponsor should be asked to determine and report the etiology of the inconsistency in response assessments between the NDA and the independent review. Based on the determination of the inconsistency, the sponsor should provide a satisfactory rationale and justification for utilizing the NDA reported response assessments or amend the NDA to utilize independent review response assessments.

- Metastatic liver disease was identified by the independent review panel in 8 subjects and in the course of my review, I found an additional subject (**451-4507**) (see **Attachment G** for a complete listing of the 9 subjects). However, inconsistent with the presence of metastatic liver disease, the clinical stage at baseline, as reported for all subjects with metastatic liver disease in the Case Report Form (CRF), is stage II or III. The sponsor should be asked to determine and report the etiology of the inconsistent staging of disease with the presence of metastatic liver disease in these 9 subjects. Incidentally noted, the metastatic disease in the 8 subjects was identified and reported by independent reviewer # 2 only. Independent reviewer # 1 did not detect metastatic liver disease in any of the 8 subjects.

- Eligibility criteria for enrollment required the presence of measurable disease. No measurable disease was reported by any independent reviewer for 20 subjects and the lack of measurable disease was confirmed in my review (see **Attachment C**). Measurable disease was not reported by at least one of the independent reviewers for an additional 37 subjects (see **Attachment D**). The sponsor should be asked to assess and report the measurable disease burden in these subjects and to confirm the eligibility status for enrollment of these subjects.

- A confirmed overall objective response was reported in 19 subjects by the independent review, however, these 19 subjects do not have documented tumor measurements to confirm and support their confirmed overall objective responses (see **Attachment E**). My review supported a confirmed overall objective response assessment in 5 of these 19 subjects, but I am unable to establish an overall objective response in 14 of these 19 subjects. In their interviews, both independent review physicians reported they had disregarded the tumor measurements in some subjects and that they had not amended the tumor measurements in accordance with their review findings. However, without recorded tumor measurements to support their interpretations, the independent reviewers provided no documented comments to justify their interpretations of a confirmed overall objective response. The sponsor should be asked to have these subjects independently reassessed to document and support the classification of these subjects as confirmed overall objective responders.

- Missing image sets were noted for 55 subjects (see **Attachment H**). Non-responders accounted for 52 subjects. However, three subjects (**502-5052, 601-6007, 851-8512**) have been reported in the NDA dataset as overall objective responders. Thus, no confirmation by the independent reviewer or by my review can be accomplished. The sponsor should be asked to obtain the CT scans for these subjects and submit them to an independent review to confirm the response assessment.

Background:

Sponsor/CRO Independent Review:

The sponsor of the NDA is Eli Lilly and the CRO performing the independent imaging review is —— . Three physicians performed the independent interpretations ad they are listed in the table below.

Reader				FDA Interview Date
1				March 6, 2003
2				February 4, 2003
3				No Visit

Dr. —— physician/pulmonary disease specialist with extensive experience in the assessment and treatment of Mesothelioma. Dr. — is a radiologist with extensive experience in the assessment of benign and malignant chest disease. Each came to my offices, with representatives of Eli Lilly and —— interpreted submitted CT scans from the independent review dataset, discussed the imaging findings reported by all independent reviewers, and assessed the imaging criteria set forth prospectively in the independent review charter.

Both physicians stated independently the following:

- The assessment criteria, as set forth in the independent review charter, are inadequate and inappropriate to assess response in some subjects. Both physicians stated that the criteria could not have been improved prospectively, due to the limited imaging experience with Mesothelioma in the medical literature. Both physicians agreed that based on the experience in this clinical trial, improved criteria for future independent reviews was now feasible.

- Both physicians stated they had disregarded the criteria set forth in the independent review charter in many cases and had applied their own subjective, undocumented, criteria to make their determination of response.

- Both physicians stated they had disregarded the imaging measurements of disease assigned by —— but the physicians stated they had not altered the imaging measurements, in accordance with their final response assessment.

- Both physicians agreed that their interpretations had resulted in inconsistencies in the final assessments dataset.

- Both physicians stated that their individual response assessments would be inconsistent in some cases with the other independent review physicians. Dr. —— stated that his orientation to response assessments for Mesothelioma is based on the available lung capacity and that he tends to disregard absolute tumor measurements, if lung capacity appeared to improve significantly. Dr. —— stated that his assessments are more closely aligned to measured tumor volumes. Dr. — stated that his assessment of tumor volume was not consistent in some cases with the . —— assessments, however, he had not documented or corrected measurements in some cases. Both physicians were aware of the other's diagnostic approach and noted that their divergent diagnostic approaches could be inconsistent in some cases.

CDER Independent Assessment:

—— loaded the independent review database on the imaging review system in my office. The system is fully functional and presented the available CT scans and the independent review findings.

Dr. White and myself reviewed subject image files during multiple review sessions over the course of two months.

The review format chosen was for Dr. White to provide a selected listing of subjects to be reviewed for each CDER review session. In the course of the review, Dr. White would identify the subject case number and I would select the case by the stated number from the imaging dataset and the independently interpret the image for tumor burden and response for the various time points. These assessments were correlated with the independent reviewer assessments documented in the imaging database.

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/s/

Patricia Garvey
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CSO

Entered in DFS for Dr. George Mills (CBER) - consulted to review NDA imaging. Review completed September 23, 2003.